

USES OF MELANOCORTIN-4 RECEPTOR (MC4R) AGONIST PEPTIDES ADMINISTERED BY CONTINUOUS INFUSION

The melanocortin-4 receptor (MC4R) is a G-protein coupled receptor (GPCR).
5 MC4R mediates a signal that it receives from the endogenous melanocortin stimulating
hormones (MSH) and the agouti related protein peptide (AGRP) in the hypothalamus.
The former peptides are processed from a proopiomelanocortin (POMC) precursor
protein produced by the neurons in the arcuate nucleus of the hypothalamus. Those
peptides are competitive full agonists for the MC4 receptor. Conversely, AGRP is
10 reported to be either a competitive antagonist or an inverse agonist at the same receptor.
This endogenous messenger is also produced and released by neurons in the
hypothalamus but distinct from those synthesizing POMC. Together, the melanocortin
system is part of the neuronal hypothalamic network regulating energy balance.

It has been proposed that during physiological states characterized by a negative
15 energy balance, AGRP signaling is enhanced and POMC signaling is reduced. Further,
those responses are thought to participate in correcting the negative energy balance.
Specifically, AGRP signaling would dominate over MSH signaling, resulting in enhanced
appetite and decreased energy expenditure via decreased activity of the sympathetic
nervous system.

20 Etiology and pathophysiology of obesity remains a subject of intense study.
There are rare examples of obese individuals and obese rodents with mutations of MC4R
or POMC genes. Over-expression of an AGRP transgene will also present an obese
mouse. There are no examples of over-expression of POMC producing a lean phenotype.
This raises the possibility that MC4R may be desensitized during continuous exposure to
25 its agonists. Indeed, there are many examples of GPCRs that are down regulated by
chronic exposure to their agonists.

Daily peripheral administration of the MSH agonist melanotan II (MT-II) for at
least one week decreases weight gain in rodents, indicating that a peripheral injection of
the peptide will trigger the MC4 receptor in the hypothalamus and that a lean phenotype
30 can be realized. Further, such studies suggest no desensitization after intermittent
administration. Because those peptides have a short half-life and were only administered

intermittently, it follows that the receptor was also only infrequently occupied and that may have prevented any down regulation or desensitization.

A need exists to find an agonist capable of triggering the MC4 receptor, capable of being administered such that the receptor remains occupied, but without down
5 regulation or desensitization of the receptor. Meeting this need will provide a means to induce weight loss and overcome obesity, a disease that has major debilitating effects on the body.

The present invention provides a method of inducing weight loss in a patient,
10 comprising continuous infusion of an effective amount of an MC4R agonist peptide into the patient. Additionally, the present invention provides a method of treating obesity in a patient, comprising continuous infusion of an effective amount of an MC4R agonist peptide into the patient. Furthermore, the present invention provides the use of an MC4R agonist peptide for the manufacture of a medicament for the treatment of obesity,
15 wherein the medicament is administered by continuous infusion.

The instant invention demonstrates that when the same mass of an MC4R agonist peptide is delivered to patients using two different methods: (1) a single daily bolus subcutaneous administration, or (2) by continuous subcutaneous infusion, the peptide is much more effective when administered continuously than intermittently. Those data
20 suggest that the MC4 receptor can be continuously occupied with an agonist without down regulation or desensitization.

Moreover, a low rate of infusion, for example approximately 2 $\mu\text{g/hr}$ of Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂ infused into the subcutaneous environment, is sufficient to overcome metabolism and dilution of the peptides to
25 successfully bind the hypothalamic receptor in quantities that would overcome competition by AGRP.

Furthermore, delivery of the peptide via continuous infusion allows the MC4 receptor to remain continuously occupied. Importantly, this overcomes problems associated with bolus injections. For instance, due to short half-life of the MC4R
30 agonist peptide, shortly after a bolus injection is made, the peptide degrades, leaving the receptor open for antagonists or inverse agonists to occupy. Occupation by an antagonist or inverse agonist may not induce weight loss; conversely, it may induce

weight gain. Yet, with continuous infusion of the MC4R agonist peptide, the receptor remains occupied with the agonist. Additionally, potential side effects caused by bolus injections, such as penile erection, may be avoided.

5 For the purposes of the present invention, as disclosed and claimed herein, the following terms are as defined below.

 “Continuous infusion” of an MC4R agonist peptide refers to controlled parenteral delivery of the peptide to a patient for an extended period of time. Administration of the peptide may be accomplished by, but is not limited to, delivery via pump, depot,
10 suppository, pessary, transdermal patch or other topical administration (such as buccal, sublingual, spray, ointment, creme, or gel) using, for example, subcutaneous, intramuscular, intraperitoneal, intravenous, intracerebral, or intraarterial administration.

 A pump delivering the MC4R agonist peptide into the body may be implanted in the patient’s body. Alternatively, the patient may wear a pump externally, being attached
15 to the patient’s body via catheter, needle, or some other connective means. Any pump that is suitable for the delivery of pharmaceuticals to a patient may be used. Examples include pumps such as those disclosed in US Pat. No. 6,659,982.

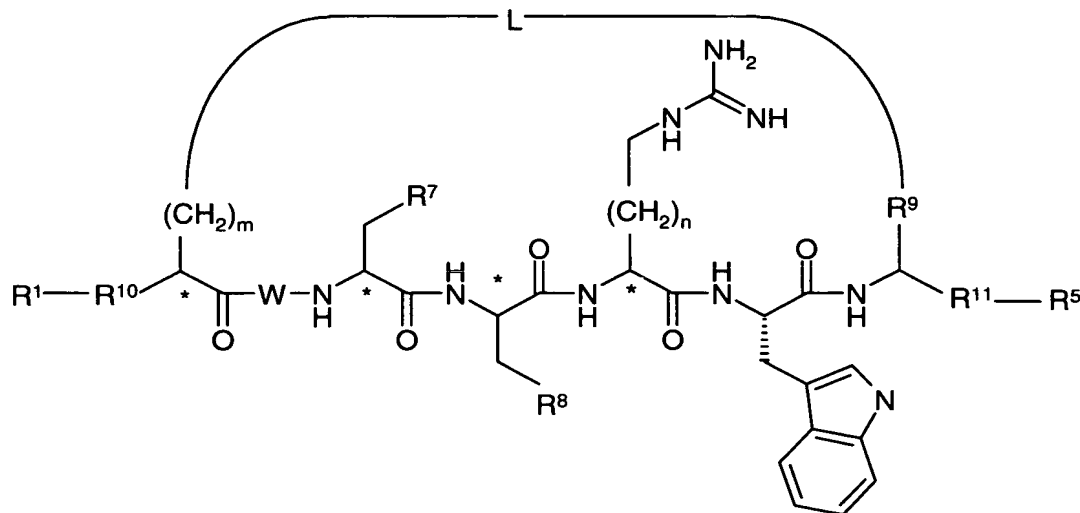
 A depot is a biocompatible polymer system containing the MC4R agonist peptide and delivering the peptide over time. Examples include microspheres, microcapsules,
20 nanoparticles, liposomes, a hydrogel, or other polymeric implants. Preferred periods for delivery of agonist by depot include one week, two weeks, and one month periods. If needed, another depot will be delivered to the patient for continued delivery of peptide.

 Engineering the MC4R agonist peptide to have a prolonged half-life will also result in continuous delivery of the MC4 receptor agonist to the receptor. Such
25 modifications include conjugations with larger proteins such as albumin, antibody and antigen or chemical modifications that may increase half-life by linking fatty acids, polyethylene glycol (PEG) polymers, and other agents.

 An “MC4R agonist peptide” utilized in the instant invention includes any agonist peptide which has affinity for the MC4 receptor. Examples include, but are not limited
30 to, MC4R agonists disclosed in the following art: US Pat. No. 5,674,839; WO 01/52880; WO 03/006604; WO 00/36136; WO 01/00224; WO 01/13112; WO 00/58361; US Pat. No. 6,613,874; WO 02/26774; WO 99/54358; WO 01/74844; WO 02/18437;

WO 98/27113; WO 01/05401; US Pat. No. 5,731,408; and WO 01/85930, which are herein incorporated by reference.

In another embodiment, the MC4R agonist peptide for use in the present invention is represented by the following Structural Formula I (SEQ ID NO:199):



and pharmaceutically acceptable salts thereof, wherein

W is Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr,
Trp, Phe, Lys, Leu, Cys, or is absent;

R^1 is -H, -C(O)CH₃, -C(O)(CH₂)₁₋₄CH₃, -C(O)(CH₂)₁₋₄NHC(NH)NH₂,

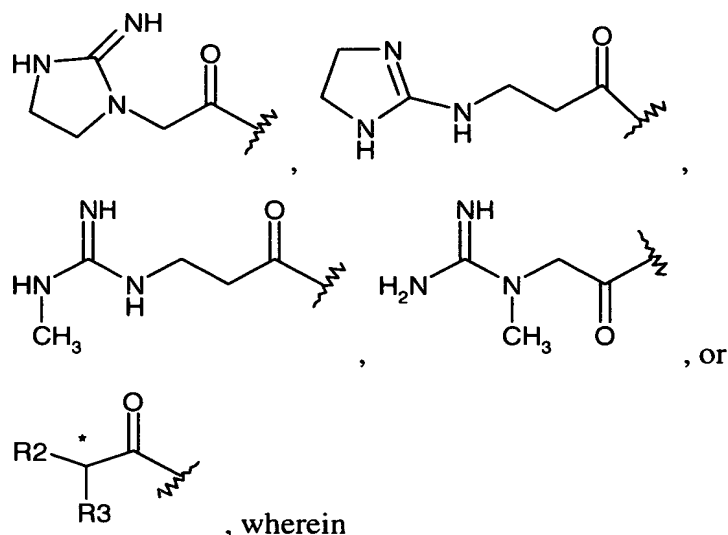
Tyr-βArg-, Ac-Tyr-β-hArg-, gluconoyl-Tyr-Arg-, Ac-diaminobutyryl-, Ac-diaminopropionyl-, N-propionyl-, N-butyryl-, N-valeryl-,

N-methyl-Tyr-Arg-, N-glutaryl-Tyr-Arg-, N-succinyl-Tyr-Arg-,

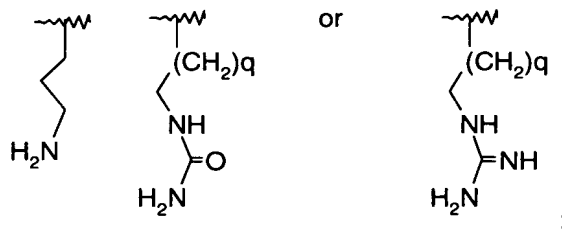
$$\text{R}^6\text{-SO}_2\text{NHC(O)CH}_2\text{CH}_2\text{C(O)-}, \text{R}^6\text{-SO}_2\text{NHC(O)CH}_2\text{CH}_2\text{C(O)Arg-},$$

$R^6-SO_2NHCH_2CH_2CH_2C(O)-$, C₃-C₇ cycloalkylcarbonyl, phenylsulfonyl,

C₈-C₁₄ bicyclic arylsulfonyl, phenyl-(CH₂)_qC(O)-, C₈-C₁₄ bicyclic aryl-(CH₂)_qC(O)-,



R^2 is -H, -NH₂, -NHC(O)CH₃, -NHC(O)(CH₂)₁₋₄CH₃,
 5 -NH-TyrC(O)CH₃, R⁶SO₂NH-, Ac-Cya-NH-, Tyr-NH-,
 HO-(C₆H₅)-CH₂CH₂C(O)NH-, or CH₃-(C₆H₅)-C(O)CH₂CH₂C(O)NH-;
 R^3 is C₁-C₄ straight or branched alkyl, NH₂-CH₂-(CH₂)_q-, HO-CH₂-,
 (CH₃)₂CHNH(CH₂)₄-, R⁶(CH₂)_q-, R⁶SO₂NH-, Ser, Ile,



10 q is 0, 1, 2, or 3;
 R^6 is a phenyl or C₈-C₁₄ bicyclic aryl;
 m is 1 or 2;
 n is 1, 2, 3, or 4;
 R^9 is (CH₂)_p or (CH₃)₂C-;
 15 p is 1 or 2;
 R^{10} is NH- or is absent;
 R^7 is a 5- or 6-membered heteroaryl or a 5- or 6-membered heteroaryl ring
 optionally substituted with R⁴;
 R^4 is H, C₁-C₄ straight or branched alkyl, phenyl, benzyl, or
 20 (C₆H₅)-CH₂-O-CH₂-;
 R^8 is phenyl, a phenyl ring optionally substituted with X, or cyclohexyl;

X is H, Cl, F, Br, methyl, or methoxy;

R^{11} is $-C(O)$ or $-CH_2$;

R⁵ is -NH₂, -OH, glycinol, NH₂-Pro-Ser-, NH₂-Pro-Lys-, HO-Ser-,

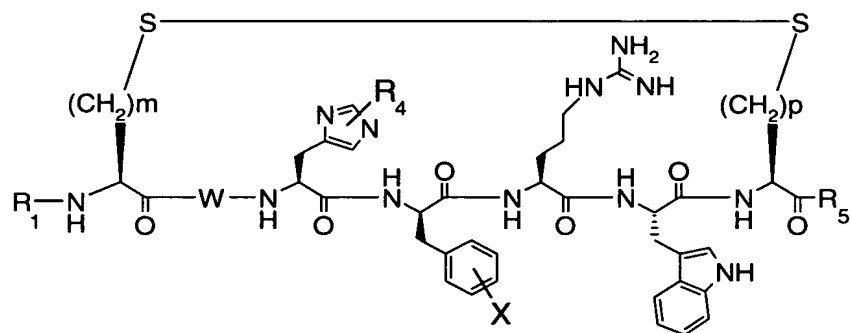
HO-Pro-Ser-, HO-Lys-, -Ser alcohol, -Ser-Pro alcohol, -Lys-Pro alcohol,

5 HOCH₂CH₂-O-CH₂CH₂NH-, NH₂-Phe-Arg-, NH₂-Glu-,

NH₂CH₂RCH₂NH-, RHN-, or RO- where R is a C₁-C₄ straight or branched alkyl; and

L is $-S-S-$ or $-S-CH_2-S-$.

10 A preferred group of MC4R agonist peptides for use in the present invention
includes compounds of Structural Formula II (SEQ ID NO:200):



and pharmaceutically acceptable salts thereof, wherein

W is Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr,

15 Trp, Phe, Lys, Leu, Cya, or is absent;

R^1 is -H, -C(O)CH₃, -C(O)(CH₂)₁₋₄CH₃, -C(O)(CH₂)₁₋₄NHC(NH)NH₂,

Tyr-βArg-, Ac-Tyr-β-hArg-, gluconoyl-Tyr-Arg-, Ac-diaminobutyryl-,

Ac-diaminopropionyl-, N-propionyl-, N-butyryl-, N-valeryl-,

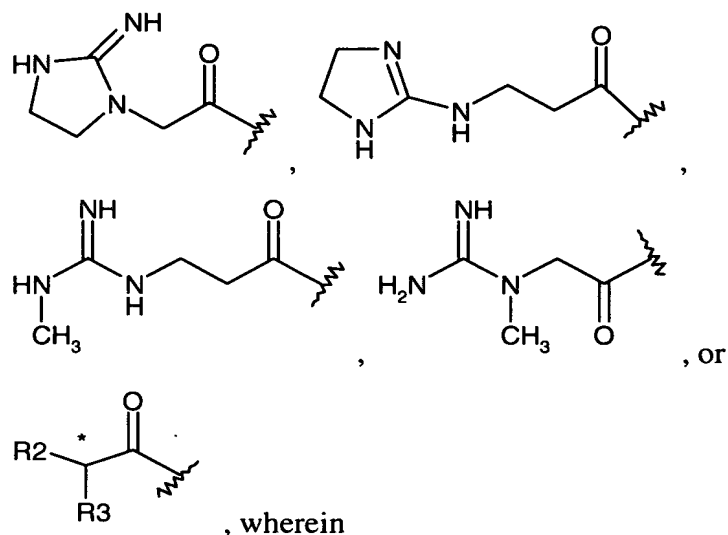
N-methyl-Tyr-Arg-, N-glutaryl-Tyr-Arg-, N-succinyl-Tyr-Arg-,

20 $R^6-SO_2NHC(O)CH_2CH_2C(O)-$, $R^6-SO_2NHC(O)CH_2CH_2C(O)Arg-$,

R⁶-SO₂NHCH₂CH₂CH₂C(O)-, C₃-C₇ cycloalkylcarbonyl, phenylsulfonyl,

C₈-C₁₄ bicyclic arylsulfonyl, phenyl-(CH₂)_qC(O)-, C₈-C₁₄ bicyclic

aryl-(CH₂)_qC(O)-,



R^2 is -H, -NH₂, -NHC(O)CH₃, -NHC(O)(CH₂)₁₋₄CH₃,

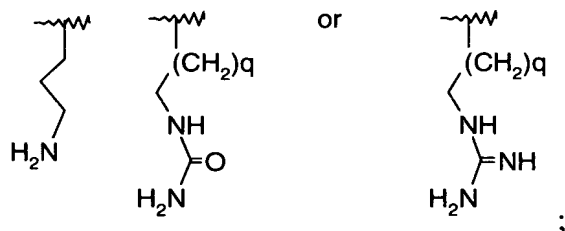
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-NH-TyrC(O)CH₃, R⁶SO₂NH-, Ac-Cya-NH-, Tyr-NH-,

HO-(C₆H₅)-CH₂CH₂C(O)NH-, or CH₃-(C₆H₅)-C(O)CH₂CH₂C(O)NH-;

R³ is C₁-C₄ straight or branched alkyl, NH₂-CH₂-(CH₂)_q-, HO-CH₂-,

(CH₃)₂CHNH(CH₂)₄-, R⁶(CH₂)_q-, R⁶SO₂NH-, Ser, Ile,



10

q is 0, 1, 2, or 3;

R⁶ is a phenyl or C₈-C₁₄ bicyclic aryl;

m is 1 or 2;

p is 1 or 2;

R⁴ is H, C₁-C₄ straight or branched alkyl, phenyl, benzyl, or

15

(C₆H₅)-CH₂-O-CH₂-;

X is H, Cl, F, Br, methyl, or methoxy; and

R⁵ is -NH₂, -OH, glycinol, NH₂-Pro-Ser-, NH₂-Pro-Lys, HO-Ser-,

HO-Pro-Ser-, HO-Lys-, -Ser alcohol, -Ser-Pro alcohol, -Lys-Pro alcohol,

HOCH₂CH₂-O-CH₂CH₂NH-, NH₂-Phe-Arg-, NH₂-Glu-,

$\text{NH}_2\text{CH}_2\text{RCH}_2\text{NH}-$, $\text{RHN}-$, or $\text{RO}-$ where R is a $\text{C}_1\text{-C}_4$ straight or branched alkyl.

Another preferred group of MC4R agonist peptides for use in the present invention are compounds of the Structural Formula II, wherein W is Glu or is absent; R_4 is H or CH_3 ; X is H, Cl, F, or Br; and R_5 is NH_2 or OH.

Yet another preferred group of MC4R agonist peptides are compounds of Structural Formula II wherein W is Glu or is absent; R^1 is H-, Ac-, Arg-, Ac-Arg-, or Ac-D-Arg-; m is 1 or 2; p is 1; and R^5 is NH_2 or OH.

10 A preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is absent; R^1 is Ac-; m is 2; p is 1; and R^5 is NH_2 .

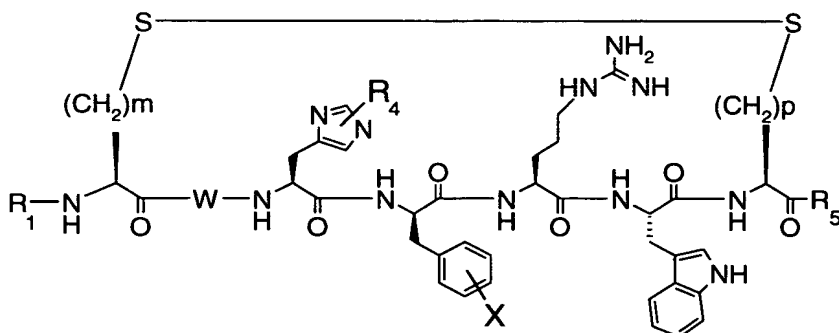
Another preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is Glu; R^1 is Ac-Arg-; m is 1; p is 1; and R^5 is NH_2 .

15 Another preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is absent; R^1 is H; m is 2; p is 1; and R^5 is NH_2 .

Another preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is absent; R^1 is Arg-; m is 2; p is 1; and R^5 is OH.

20 A most preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is Glu; R^1 is Ac-D-Arg-; m is 1; p is 1; and R^5 is NH_2 .

An alternative preferred group of MC4R agonist peptides for use in the present invention is represented by the following Structural Formula III (SEQ ID NO:201):

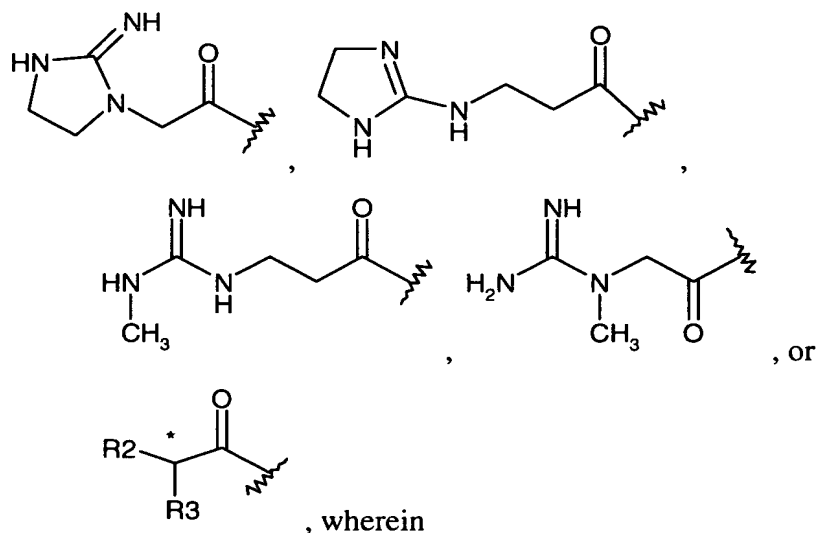


5 and pharmaceutically acceptable salts thereof, wherein

W is a single bond, Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, or Phe;

R₁ is -H, -C(O)CH₃, -C(O)(CH₂)₁₋₄NH-C(NH)NH₂, Tyr-βArg,

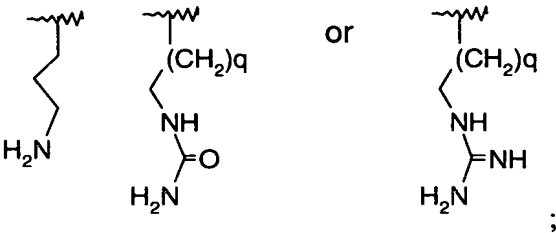
gluconoyl-Tyr-Arg, Ac-Dab, Ac-Dap, N-succinyl-Tyr-Arg, N-propionyl,
10 N-valeryl, N-glutaryl-Tyr-Arg, N-butyryl,



15

R₂ is -H, -NH₂, -NHC(O)CH₃, -NHC(O)(CH₂)₁₋₄CH₃, Tyr, or
-NH-Tyr-C(O)CH₃;

R₃ is C₁-C₄ straight or branched alkyl, Ser, Ile, Arg,



q is 0, 1, 2, or 3;
m is 1 or 2;
p is 1 or 2;
R₄ is -H, -CH₃, or -(CH₂)₁₋₃CH₃;
X is -H, -Cl, -F, -Br, methyl, or methoxy; and
R₅ is -NH₂, -OH, glycinol, -Ser-Pro-NH₂, -Lys-Pro-NH₂, -Ser-OH,
-Ser-Pro-OH, -Lys-Pro-OH, -Arg-Phe-NH₂, -Glu-NH₂, -NHR, or -OR,
where R is -CH₃ or -(CH₂)₁₋₃CH₃.

MC4R agonist peptides for use in the present invention include, but are not limited to, those compounds listed in the following table:

Table 1. Specific compounds within the present invention.

No.	Name
1	Ac-cyclo[Cys-His-D-Phe-Arg-Trp-Cys]-NH ₂
2	Ac-Cya-Arg-cyclo[Cys-Ala-His-D-Phe-Arg-Trp-Cys]-NH ₂
3	Ac-Tyr-Arg-cyclo[Cys-Ala-His-D-Phe-Arg-Trp-Cys]-NH ₂
4	Ac-Tyr-Arg-cyclo[Cys-Arg-His-D-Phe-Arg-Trp-Cys]-NH ₂
5	Ac-Tyr-Arg-cyclo[Cys-Asn-His-D-Phe-Arg-Trp-Cys]-NH ₂
6	Ac-cyclo[Cys-Asp-His-D-Phe-Arg-Trp-Cys]-NH ₂
7	Ac-Tyr-Arg-cyclo[Cys-Asp-His-D-Phe-Arg-Trp-Cys]-NH ₂
8	Ac-cyclo[Cys-Gln-His-D-Phe-Arg-Trp-Cys]-NH ₂
9	Ac-Tyr-Arg-cyclo[Cys-Gln-His-D-Phe-Arg-Trp-Cys]-OH
10	Ac-Tyr-Arg-cyclo[Cys-Gln-His-D-Phe-Arg-Trp-Cys]-OMe
11	Tyr-Arg-cyclo[Cys-Gly-His-D-Phe-Arg-Trp-Cys]-NH ₂
12	Ac-Tyr-Arg-cyclo[Cys-Gly-His-D-Phe-Arg-Trp-Cys]-NH ₂
13	Ac-Tyr-Arg-cyclo[Cys-His-His-D-Phe-Arg-Trp-Cys]-NH ₂
14	Ac-Tyr-Arg-cyclo[Cys-Ile-His-D-Phe-Arg-Trp-Cys]-NH ₂
15	Ac-cyclo[Cys-Leu-His-D-Phe-Arg-Trp-Cys]-NH ₂
16	Ac-cyclo[Cys-Lys-His-D-Phe-Arg-Trp-Cys]-NH ₂
17	N-methyl-Tyr-Arg-cyclo[Cys-Met-His-D-Phe-Arg-Trp-Cys]-NH ₂
18	Ac-Tyr-Arg-cyclo[Cys-Met-His-D-Phe-Arg-Trp-Cys]-NH ₂
19	Ac-Tyr-Arg-cyclo[Cys-Phe-His-D-Phe-Arg-Trp-Cys]-NH ₂
20	Ac-Tyr-Arg-cyclo[Cys-Pro-His-D-Phe-Arg-Trp-Cys]-NH ₂

No.	Name
21	Ac-Tyr-Arg-cyclo[Cys-Ser-His-D-Phe-Arg-Trp-Cys]-NH ₂
22	Ac-Tyr-Arg-cyclo[Cys-Thr-His-D-Phe-Arg-Trp-Cys]-NH ₂
23	Ac-Tyr-Arg-cyclo[Cys-Trp-His-D-Phe-Arg-Trp-Cys]-NH ₂
24	Ac-Tyr-Arg-cyclo[Cys-Tyr-His-D-Phe-Arg-Trp-Cys]-NH ₂
25	Ac-Tyr-Arg-cyclo[Cys-Val-His-D-Phe-Arg-Trp-Cys]-NH ₂
26	Ac-Arg-cyclo[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH ₂
27	Ac-D-Arg-cyclo[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH ₂
28	Ac-Tyr-Arg-cyclo[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH ₂
29	cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
30	Ac-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
31	Ac-cyclo[Cys-Glu-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH ₂
32	Ac-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH ₂
33	Ac-cyclo[Cys-Glu-His-(4-Br-D-Phe)-Arg-Trp-Cys]-NH ₂
34	Ac-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
35	Ac-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro-NH ₂
36	Ac-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH ₂
37	N-propionyl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
38	N-butyryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
39	N-valeryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
40	3-guanidinopropionyl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
41	4-guanidinobutyryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
42	5-guanidinovaleryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
43	Ac-diaminopropionyl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
44	Ac-diaminobutyryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
45	Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
46	D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
47	Ac-D-Arg-cyclo[Cys-Glu-His-Phe-Arg-Trp-Cys]-NH ₂
48	Ac-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
49	Ac-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
50	Ac-Arg-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH ₂
51	Ac-Arg-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
52	Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
53	Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
54	Ac-hArg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
55	Ac-Cit-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
56	Ac-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
57	Ac-Leu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
58	Ac-Lys-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
59	Ac-Lys(ipr)-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
60	Ac-nLeu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
61	Ac-nLeu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH ₂
62	Ac-Orn-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
63	Ac-Val-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
64	N-(2-naphthalenesulfonyl)-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
65	N-(2-naphthalenesulfonylamino-4-oxo-butyryl)-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
66	3-(4-hydroxyphenyl)propionyl-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
67	3-(4-methylbenzoyl)propionyl-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂

No.	Name
68	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
69	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
70	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH-(CH ₂) ₆ -NH ₂
71	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Glu-NH ₂
72	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
73	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
74	N-succinyl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
75	N-glutaryl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
76	N-glutaryl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
77	gluconoyl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
78	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys] alcohol
79	Ac-Tyr-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
80	Ac-Tyr-Arg-cyclo[D-Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
81	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
82	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH ₂
83	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH ₂
84	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-F-D-Phe)-Arg-Trp-Cys]-NH ₂
85	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-F-D-Phe)-Arg-Trp-Cys]-NH ₂
86	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH ₂
87	Ac-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH ₂
88	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH ₂
89	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Br-D-Phe)-Arg-Trp-Cys]-NH ₂
90	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-Br-D-Phe)-Arg-Trp-Cys]-NH ₂
91	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-Br-D-Phe)-Arg-Trp-Cys]-NH ₂
92	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Me-D-Phe)-Arg-Trp-Cys]-NH ₂
93	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-OMe-D-Phe)-Arg-Trp-Cys]-NH ₂
94	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-OMe-D-Phe)-Arg-Trp-Cys]-NH ₂
95	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-OMe-D-Phe)-Arg-Trp-Cys]-NH ₂
96	Ac-Tyr-Arg-cyclo[Cys-Glu-(3-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
97	Ac-Tyr-Arg-cyclo[Cys-Glu-(5-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
98	Ac-Tyr-Arg-cyclo[Cys-Glu-(5-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH ₂
99	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-benzyl-His)-D-Phe-Arg-Trp-Cys]-NH ₂
100	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-benzyl-D-His)-D-Phe-Arg-Trp-Cys]-NH ₂
101	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Bom-His)-D-Phe-Arg-Trp-Cys]-NH ₂
102	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-pyrazolyl-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
103	Ac-Tyr-Arg-cyclo[Cys-Glu-(4-phenyl-1H-imidazol-2-yl-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
104	Ac-Tyr-Arg-cyclo[Cys-Glu-(4-phenyl-1H-imidazol-2-yl-D-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
105	Ac-Tyr-Arg-cyclo[Cys-Glu-(2-pyrazine-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
106	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1,2,4-triazol-3-yl))-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
107	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1,2,4-triazol-3-yl))-D-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
108	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-((1-benzyl)-1,2,4-triazol-3-yl))-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
109	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-((1-benzyl)-1,2,4-triazol-3-yl))-D-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
110	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(2-furyl)-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
111	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(thien-2-yl)-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
112	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(1,3-thiazol-4-yl)-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
113	Ac-Tyr-Arg-cyclo[Cys-Glu-(β-(pyridin-4-yl)-Ala)-D-Phe-Arg-Trp-Cys]-NH ₂
114	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-glycinol
115	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-2-(2-aminoethoxy)ethanol

No.	Name
116	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser alcohol
117	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH-(CH ₂) ₆ -NH ₂
118	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Glu-NH ₂
119	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH ₂
120	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro alcohol
121	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro-NH ₂
122	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro alcohol
123	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Arg-Phe-NH ₂
124	Ac-Tyr-Cit-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
125	Ac-Tyr-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
126	Ac-Tyr-hArg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
127	Ac-Tyr-(1-β-hArg)-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
128	Ac-Tyr-Lys-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
129	Ac-Tyr-Ser-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
130	Ac-Tyr-Val-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
131	N-succinyl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
132	cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
133	cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
134	cyclo[hCys-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH ₂
135	cyclo[hCys-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH ₂
136	Ac-cyclo[hCys-His-Phe-Arg-Trp-Cys]-NH ₂
137	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
138	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
139	Ac-cyclo[hCys-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH ₂
140	Ac-cyclo[hCys-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH ₂
141	N-cyclopropanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
142	N-cyclobutanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
143	N-cyclopentanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
144	N-cyclohexanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
145	N-hexanoyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
146	N-benzoyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
147	4-phenylbutyryl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
148	3-guanidinopropionyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
149	5-guanidinovaleryl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
150	N-phenylsulfonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
151	N-(2-naphthalenesulfonyl)-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
152	N-(4-phenylsulfonamido-4-oxo-butyl)-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
153	Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
154	D-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
155	Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
156	Arg-cyclo[hCys-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH ₂
157	Arg-cyclo[hCys-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH ₂
158	Ac-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
159	Ac-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
160	Ac-nLeu-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
161	phenylsulfonyl-Gly-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
162	Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
163	Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH

No.	Name
164	Ac-Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH ₂
165	Ac-Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
166	Ac-Tyr-Arg-cyclo[hCys-Glu-His-D-Phe-Arg-Trp-Cys]-NH ₂
167	Ac-cyclo[hCys-His-(8-cyclohexyl-D-Ala)-Arg-Trp-Cys]-NH ₂
168	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
169	Ac-cyclo[hCys-His-(4-Cl-D-Phe)-Arg-Trp-penicillamine]-NH ₂
170	N-hexanoyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
171	N-cyclopentanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
172	N-cyclohexanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
173	N-benzoyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
174	4-phenylbutyryl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
175	N-phenylsulfonyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
176	(4-benzenesulfonamide)butyryl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
177	Ac-nLeu-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
178	N-phenylsulfonyl-Gly-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH ₂
179	cyclo[3-thiopropionyl-His-D-Phe-Arg-Trp-hCys]-NH ₂
180	cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH ₂
181	cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH ₂
182	cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH ₂
183	Ac-cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH ₂
184	Ac-cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH ₂
185	Ac-cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH ₂
186	Arg-cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH ₂
187	Arg-cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH ₂
188	Arg-cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH ₂
189	Ac-Arg-cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH ₂
190	Ac-Arg-cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH ₂
191	Ac-Arg-cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH ₂
192	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-hCys]-NH ₂
193	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH ₂
194	Arg-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH ₂
195	Ac-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH ₂
196	Ac-Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH ₂
197	Ac-Tyr-Arg-cyclo[hCys-Glu-His-D-Phe-Arg-Trp-hCys]-NH ₂
198	Ac-cyclo(S-CH ₂ -S)[Cys-His-D-Phe-Arg-Trp-Cys]-NH ₂

A preferred group for use in the invention includes MC4R agonist peptides having Compound Nos. 48, 52, 132, 137, and 155. More preferred is a group consisting of Compound Numbers 52 and 137. A more preferred compound for use in the present invention is Compound Number 137, denoted by the name Ac-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH₂, as the MC4R agonist peptide. A most preferred compound for use in the present invention is Compound Number 52, denoted by the name Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂, as the MC4R agonist peptide.

As used herein, "C₁-C₄ straight or branched alkyl" means a straight chained or branched hydrocarbon having 1 to 4 carbon atoms, which is completely saturated and

unsubstituted. "C₃-C₇ cycloalkyl" refers to a saturated, unsubstituted hydrocarbon ring having 3 to 7 carbon atoms. A "C₁-C₄ straight or branched heteroalkyl" refers to a straight chained or branched hydrocarbon having 1 to 4 carbon atoms, which is completely saturated and unsubstituted, that also contains at least one "heteroatom." A
5 "heteroatom" is nitrogen, oxygen, or sulfur. "C₃-C₇ heterocycloalkyl" refers to a saturated, unsubstituted hydrocarbon ring having 3 to 7 carbon atoms, which also contains at least one "heteroatom." C₁-C₄ straight or branched alkyl, C₃-C₇ cycloalkyl, C₁-C₄ straight or branched heteroalkyl, and C₃-C₇ heterocycloalkyl may be used as generic modifiers to describe a genus of substituents on another functional group such as a
10 carbonyl, sulfonyl, or sulfonamide. For example, a "C₃-C₇ cycloalkylcarbonyl" refers to a genus of saturated, unsubstituted hydrocarbon rings having 3 to 7 carbon atoms that are bonded to a carbonyl group.

A "C₈-C₁₄ bicyclic aryl" refers to two or three hydrocarbon rings fused together, having 8 to 14 carbon atoms, such as naphthalene. A C₈-C₁₄ bicyclic aryl ring system has
15 at least one aromatic ring. A "5- or 6-membered heteroaryl" refers to a monocyclic aromatic ring having 5 or 6 atoms, of which 1-4 atoms are heteroatoms. An "8- to 14-membered bicyclic heteroaryl" ring refers to two or three hydrocarbon rings fused together, having 8 to 14 atoms, at least one aromatic ring, and 1-4 heteroatoms.

A phenyl, benzyl, benzoyl, C₈-C₁₄ bicyclic aryl, 5- or 6-membered heteroaryl, or
20 8- to 14-membered bicyclic heteroaryl may be unsubstituted or substituted with C₁-C₄ straight or branched alkyl, F, Cl, Br, -OH, methoxy, phenyl, benzyl, benzoyl, or benzyloxymethyl. Furthermore, phenyl, benzyl, benzoyl, C₈-C₁₄ bicyclic aryl, 5- or 6-membered heteroaryl, and 8- to 14-membered bicyclic heteroaryl may be used as generic modifiers to describe a genus of substituents on another functional group such as
25 a carbonyl, sulfonyl, or sulfonamide. For example, a "C₈-C₁₄ bicyclic arylsulfonyl" refers to a genus of bicyclic aryl rings having 8 to 14 carbon atoms that are bonded to a sulfonyl group.

Modified amino acids are indicated by parentheses around the amino acid and the modification thereto (*e.g.*, (4-Cl-D-Phe) is a 4-chloro modification on the D-isomer of
30 phenylalanine). With respect to moieties depicted in Structural Formula I, Structural Formula II, and Structural Formula III, the single letter designations are as defined and do not refer to single letter amino acids corresponding to those letters.

The letter "D" preceding the above-mentioned 3-letter abbreviations, *e.g.*, "D-Phe," means the D-form of the amino acid. When the single letter abbreviation is used for an amino acid, a "d" will precede the letter to designate the D-form of the amino acid (*e.g.*, dF = D-Phe).

5 An "amino alcohol" is an amino acid that has been modified by reducing the carbonyl group of the C-terminus to a methylene group. Amino alcohols are denoted by the general nomenclature "Xaa alcohol," wherein Xaa is the specific amino acid from which the carbonyl group has been removed. To illustrate, "Ser alcohol" has the structure $\text{H}_2\text{N}-\text{CH}(\text{CH}_2\text{OH})-\text{CH}_2\text{OH}$ as opposed to the Ser amino acid structure of $\text{H}_2\text{N}-\text{CH}(\text{CH}_2\text{OH})-\text{COOH}$.

10 "Single bond," as used herein, refers to a structure that does not contain an amino acid at the specified position. It is used to signify that an amino acid is absent from that position such that the carbonyl adjacent to that position on one side and the amine adjacent to that position on the other side form a peptide bond with each other.

15 "*" means that both the D- and L- isomers are possible.

 "Ac" refers to acetyl (*i.e.*, $-\text{C}(\text{O})\text{CH}_3$).

 "Orn" refers to ornithine.

 "hCys" refers to homocysteine.

 "hArg" refers to homoarginine.

20 "Lys(ipr)" refers to lysine(N-isopropyl).

 "Cit" refers to citrulline.

 "nLeu" refers to norleucine.

 "Me" refers to methyl.

 "OMe" refers to methoxy.

25 "Cya" refers to cysteic acid.

 "Dap" refers to diaminopropionyl.

 "Dab" refers to diaminobutyryl.

 "Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I, Structural Formula II, or Structural Formula III that are substantially
30 non-toxic to mammals. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base

addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

5 A pharmaceutical "acid addition salt" is a salt formed by reaction of the free base form of a compound of formula I with a pharmaceutical acid, such as described in the Encyclopedia of Pharmaceutical Technology, editors James Swarbrick and James C. Boylan, Vol. 13 (1996), "Preservation of Pharmaceutical Products to Salt Forms of Drugs and Absorption." Specific salt forms include, but are not limited to the: acetate, benzoate, 10 benzenesulfonate, 4-chlorobenzenesulfonate; citrate; ethanesulfonate; fumarate; d-gluconate; d-glucuronate; glutarate; glycolate; hippurate; hydrochloride; 2-hydroxyethanesulfonate; dl-lactate; maleate; d-malate; l-malate; malonate; d-mandelate; l-mandelate; methanesulfonate; 1,5-naphthalenedisulfonate; 2-naphthalenesulfonate; phosphate; salicylate; succinate; sulfate; d-tartrate; l-tartrate; and p-toluenesulfonate.

15 A pharmaceutical "base addition salt" is a salt formed by reaction of the free acid form of a compound of formula I with a pharmaceutical base, such as described in the Encyclopedia of Pharmaceutical Technology, *supra*. Specific salt forms include, but are not limited to the: calcium, diethanolamine, diethylamine, ethylenediamine, lysine, magnesium, piperazine, potassium, sodium, and tromethamine (Tris, Trizma) salts.

20 The term "active ingredient" means the MC4R agonist peptides generically described by Structural Formula I, Structural Formula II, and Structural Formula III, as well as the salts of such compounds.

 The term "pharmaceutically acceptable" means that the carrier, diluent, excipients, and salt must be compatible with the other ingredients of the composition and not 25 clinically deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well-known and readily available ingredients.

 The term "agonist" includes any molecule that has affinity for the MC4 receptor, producing a measurable biological activity associated with weight loss in cells, tissues 30 and organisms containing the MC4 receptor. In a similar manner, an "inverse agonist" includes any molecule that has affinity for the MC4 receptor, producing a decreased intrinsic activity of the cell containing the MC4 receptor and is associated with weight

gain in cells, tissues, and organisms containing the MC4 receptor. The term “antagonist” includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of the MC4 receptor. Assays measuring such activities are well known in the art.

5 The term “weight loss” includes any decrease in the mass of a patient. Weight loss may include overall loss of mass by the patient or, alternatively, loss of fat mass by the patient.

The term “obesity,” also called corpulence or fatness, is the excessive accumulation of body fat, usually caused by the consumption of more calories than the body uses. The excess calories are then stored as fat, or adipose tissue. Overweight, if
10 moderate, is not necessarily obesity, particularly in muscular or large-boned individuals. In general, however, a body weight twenty percent or more over the optimum tends to be associated with obesity.

A “subject” or “patient” is a mammal, preferably a human. Nonetheless, other mammals may be subjects or patients, including companion animals such as dogs and
15 cats, laboratory animals such as rats, mice, monkeys, and guinea pigs, and farm animals such as cows, sheep, pigs, and horses.

The term “a patient in need thereof” is a patient either suffering from the claimed pathological condition or sequela thereof or is a patient at a recognized risk thereof as determined by medical diagnosis, *i.e.*, as determined by the attending physician.

20 The terms “treating,” “treatment,” and “therapy” as used herein refer to the management and care of a patient for the purpose of combating the disease, condition, or disorder. Treating includes the administration of an MC4R agonist peptide to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder. Treating obesity therefore includes the
25 inhibition of food intake, the inhibition of weight gain, and inducing weight loss in patients in need thereof.

Treatment may include curative therapy, prophylactic therapy, and preventive therapy. An example of “preventive therapy” is the prevention or lessened targeted pathological condition or disorder. Those in need of treatment include those already with
30 the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

A “therapeutically-effective amount” is the minimal amount of MC4R agonist peptide necessary to induce weight loss. An “effective amount” of the peptide administered to a subject will also depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The recipient patient’s physician should determine the therapeutic dose administered in light of the relevant circumstances.

A therapeutically-effective amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount, when administered prophylactically to a patient, can also be effective to prevent or lessen the severity of the mediated condition. The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age and sex of the recipient patient. However, it will be understood that the therapeutic dose administered will be determined by the attending physician in the light of the relevant circumstances.

Generally, an effective minimum daily dose of a compound of the present invention will exceed about 0.01 mg. Typically, an effective maximum daily dose will not exceed about 1000 mg. More preferably, an effective minimum daily dose will be between about 0.05 mg and 50 mg, more preferably between 0.1 mg and 10 mg. Most preferably, an effective minimum daily dose of an MC4R agonist peptide in the present invention will exceed about 2 µg/kg and will not exceed about 20 µg/kg. The exact dose may be determined, in accordance with the standard practice in the medical arts of “dose titrating” the recipient; that is, initially administering a low dose of the compound, and gradually increasing the dose until the desired therapeutic effect is observed. The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals.

The peptides used in the invention may be chemically synthesized. Such methods for synthesis are well known in the art.

Example 1: Comparison of Continuous Infusion of MC4R Agonist Peptide
Versus Daily Subcutaneous Injection

For this type of experiment, two solutions are prepared. First, a 5% dextrose solution is prepared by diluting 5 mL 50% dextrose solution (Biomed) in 45 mL of sterile water for injection. This dextrose solution is subsequently referred to as “vehicle.” Second, a stock solution of the MC4R agonist peptide (“P1”) to be administered subcutaneously is prepared by dissolving 1.75 mg of P1 in 2 mL of the vehicle. This stock solution is then diluted to 0.088 mg/mL using that vehicle. This solution is subsequently referred to as P1sc solution. Both the P1sc solution and the vehicle are prepared fresh every three days and stored at 4°C in a sterile capped vial throughout the experiment. A separate solution of MC4R agonist peptide is prepared for continuous infusion using osmotic pumps by dissolving 11.1 mg of P1 in 3 mL of vehicle [3.7 mg/mL]. This solution is subsequently referred to as P1p solution. Ten ALZET® mini-osmotic pumps (implantable infusion pumps that continuously deliver materials to laboratory animals; Model 2002, 14-day payout at 0.5 µL/hour) are loaded using aseptic technique with either 200 µL P1p (n=5) or vehicle (n=5) solution and allowed to prime overnight in sterile 0.9% saline at 37°C in preparation for implantation into rats.

Twenty rats are selected for this experiment. Ten rats are anaesthetized briefly with isoflurane (3%, Abbott Laboratories). Each anaesthetized rat is implanted with an ALZET® pump using sterile technique. The rats are divided into four groups of five rats: two groups containing pumps and two groups with no pumps. Experimental samples are administered to the rats as follows:

Table 1. Administration scheme for a P1 study.

Group	Substance	Delivery method	Approximate daily dose (µg/kg active)
1	MC4-R peptide P1	Sustained release via pump	44
2	Vehicle	Sustained release via pump	0
3	MC4-R peptide P1	Daily subcutaneous injection	44
4	Vehicle	Daily subcutaneous injection	0

Each rat is weighed initially, and measurements of body composition are made for each animal using QNMR (quantitative nuclear magnetic resonance). Body mass is measured daily for fourteen days, and the cumulative change in body mass is calculated. Body composition is measured again at the end of the study.

- 5 Using a procedure such as that described above, results shown in Tables 2, 3, and 4, below, may be achieved.

Table 2. Change in body mass among groups.

	Mean change in body mass (g)			
Day	Group 1	Group 2	Group 3	Group 4
1	-7.66	4.14	-0.68	2.96
2	-8.52	6.20	1.64	3.26
3	-10.12	6.70	0.46	5.68
4	-9.54	7.32	0.78	8.50
5	-12.56	8.06	1.16	10.06
6	-14.02	7.74	0.94	10.51
7	-12.86	7.88	0.80	10.90
8	-14.42	10.22	4.00	11.38
9	-14.60	9.88	2.72	14.48
10	-14.72	10.90	2.98	14.46
11	-13.04	13.86	4.28	17.24
12	-12.22	17.46	7.30	19.64
13	-9.66	18.70	9.52	20.66
14	-9.12	20.32	9.54	23.22

10 Table 3. Change in fat mass among groups.

	Mean fat mass (g)			
Day	Group 1	Group 2	Group 3	Group 4
0	78.171	81.725	74.252	81.312
14	69.273	89.887	72.912	93.182
Change	-8.898	8.162	-1.340	11.870

Table 4. Change in lean mass among groups.

	Mean lean mass (g)			
Day	Group 1	Group 2	Group 3	Group 4
0	328.609	329.489	340.206	333.134
14	330.373	344.131	353.033	344.527
Change	1.764	14.642	12.827	11.393

Additionally, the food intake of each animal (mass of food the animal eats in one day) is measured daily during the fourteen-day experiment. Results of this study are shown in Table 5, below.

5 Table 5. Food intake among groups (P1).

Day	Mean daily food intake (g)			
	Group 1	Group 2	Group 3	Group 4
1	6.76	15.98	13.76	16.06
2	10.40	19.22	15.64	19.40
3	15.14	21.36	17.58	22.18
4	14.48	20.16	15.90	20.48
5	12.20	18.26	15.94	18.50
6	12.44	16.84	14.12	17.78
7	13.96	16.70	16.70	18.68
8	14.94	17.96	16.44	16.04
9	14.22	17.48	13.24	17.58
10	16.26	18.18	17.52	17.84
11	15.70	18.36	15.46	17.62
12	15.08	16.94	16.10	17.34
13	16.76	17.78	16.30	17.40
14	14.64	17.16	15.62	16.36

Continuous subcutaneous infusion of P1 in rats results in improved efficacy over single daily bolus dosing of equivalent P1 [0.044 mg/kg]. Cumulative weight loss in rats infused with P1 is significantly increased over both vehicle treated groups and rats dosed once daily. Decreased fat mass in rats continuously infused with peptide also indicates improved efficacy over daily dosing; however, the change does not reach significance between infused and daily dosed groups.

Experiments such as that described above may be performed on other MC4R agonists and for different time periods. For example, a seven-day study administering another peptide ("P2") may be performed. A stock solution of the MC4R peptide to be dose subcutaneous is prepared by dissolving 2 mg of P2 in 2 mL of the vehicle. This stock solution is then diluted 0.1 mg/mL using vehicle. This solution is subsequently referred to as P2sc solution. Both the P2sc solution and the vehicle are prepared fresh every three days and stored at 4°C in a sterile capped vial throughout the experiment. A second solution of the MC4R peptide P2 is prepared by dissolving 5 mg of P2 in 2.4 mL

of the vehicle prepared above. This solution is subsequently referred to as P2p solution. Ten ALZET[®] mini-osmotic pumps (Model 2001, 7-day payout at 1.0 μ L/hour) are loaded using aseptic technique with either 200 μ L P2 (n=4) or vehicle (n=4) solution and allowed to prime overnight in sterile 0.9% saline at 37°C in preparation for

5 implantation into rats.

Sixteen rats are selected for this experiment. Ten rats are anaesthetized briefly with isoflurane (prepared above). Each anaesthetized rat is implanted with an ALZET[®] pump using sterile technique. The rats are divided into four groups of four rats: two groups containing pumps and two groups with no pumps. Experimental samples are

10 administered to the rats as follows:

Table 6. Administration scheme for a P2 study.

Group	Substance	Delivery method	Approximate daily dose (μ g/kg active)
1	MC4-R peptide P2	Sustained release via pump	50
2	Vehicle	Sustained release via pump	0
3	MC4-R peptide P2	Daily subcutaneous injection	50
4	Vehicle	Daily subcutaneous injection	0

Body mass is measured daily for seven days, and the cumulative change in body mass is calculated.

15 Using a procedure such as that described above, results shown in Table 7, below, may be achieved.

Table 7. Change in body mass among groups (P2).

Day	Mean change in body mass (g)			
	Group 1	Group 2	Group 3	Group 4
1	-5.52	7.03	5.50	5.88
2	-3.95	8.20	9.63	7.92
3	-10.53	1.30	5.20	4.72
4	-8.85	3.80	5.55	6.77
5	-11.35	2.60	7.43	8.82
6	-11.75	4.90	8.65	11.05
7	-13.73	6.60	9.73	12.88

Additionally, the food intake of each animal (mass of food the animal eats in one day) is measured daily during the seven-day experiment. Results of this study are shown in Table 8, below.

Table 8. Food intake among groups (P2).

Day	Mean daily food intake (g)			
	Group 1	Group 2	Group 3	Group 4
1	16.05	22.83	19.33	23.38
2	15.78	20.03	17.75	21.98
3	15.43	16.03	15.85	20.88
4	12.08	13.83	16.75	15.75
5	13.15	16.28	14.83	22.25
6	13.75	17.23	14.90	15.95
7	13.63	17.95	16.68	18.35

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Continuous subcutaneous infusion of P2 in rats supports P1 study results. Infusion of peptide improved efficacy over single daily bolus dosing of equivalent P2 [0.05 mg/kg]. Cumulative weight loss in rats infused with P2 is significantly increased over both vehicle treated groups and rats dosed once daily.